History of basal cell carcinoma and its treatment[1]

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Basal cell carcinoma is the commonest form of skin cancer. Long before its actual definition, tumours fitting its description had been recorded. Early physicians noted that whereas complete removal of the tumour gave excellent results, incomplete removal was followed by recurrences which in some cases were exceedingly difficult to treat. There is evidence that cautery, a contemporary method of treatment, has been used successfully since very early days.

Evidence for the use of cautery in the treatment of skin diseases is found in the Edwin Smith Papyrus (Breasted 1930), said to have been compiled about 2500 BC from records even older. In 1862 an American Egyptologist named Edwin Smith encountered, in Thebes, an Arab called Mustapha Aga, who sold him two papyri. One papyrus was no more than an assemblage of fragments glued together. Undaunted, Edwin Smith deciphered this papyrus and found a series of medical case histories, each one neatly documented. Most were head injuries. Expert bandaging with linen strips (learned from the embalmers) is described, as is stitching ('Thou shoulds't draw together for him his gash with stitching'). In one patient, with unidentified tumours or ulcers on the breast, treatment with the 'fire-stick' was used. The hieroglyph (𓇋) depicts a stick and a hollow block of wood, used by whirling the stick between the palms to produce friction, thus causing heat. When the end of the fire-stick was glowing, it was applied to the tumour – an early example of a form of cautery.

Two thousand years later, while the power of Egypt declined, that of the Greeks emerged and in 46 BC Hippocrates was born on the Greek island of Cos. He founded a school of medical thought which depended on accurate observation and recording of the signs, symptoms and progress of disease, and the adoption of such remedial methods as could do no harm, thus fostering the 'healing power of nature'. He did not define skin cancer, but from Hippocrates' book of Aphorisms (Lloyd 1978) the following quotations are of interest:

'Ulcers lasting a year or longer cause the underlying bone to be eaten away and the resulting scars are depressed.'
'What drugs will not cure, the knife will; what the knife will not cure, the cautery will; what the cautery will not cure must be considered incurable.'

It is uncertain whether Celsus (30 BC–AD 50), the great Roman scholar who wrote 'De Re Medicina', was medically qualified or simply a very enquiring, scholarly, and accurate observer, but he did say some interesting things about skin cancer (Spencer 1935):

'A carcinoma . . . This disease occurs mostly in the upper parts of the body, in the region of the face, nose, ears, lips . . . there is a fixed irregular swelling, sometimes there is also numbness. Around it are dilated tortuous veins.'

He stated that only in the first stages was removal possible, whilst in later stages carcinoma was irritated by treatment. As to modes of treatment, 'some have used caustic medicaments, some the cautery, some excision with a scalpel'. The writings of this Roman have put on record that in his day skin cancer was recognized, that attempts were made to remove it, and that complete eradication of the tumour was sometimes found impossible.

The Greek tradition of rational thought is still important today, but during the later centuries of Roman power, theory drifted away from observation and experiment. Ideas without truth came to be taught, accepted, and believed. There was no advance in medical science. Galen (*c.* AD 130–200), physician to the Roman emperor Marcus Aurelius, was a

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dogmatic teacher and had great influence. His theories of human anatomy were based on the dissection of apes and swine, as religious beliefs at that time did not allow human dissection. Eight hundred years after his death, Galen's theories were still being taught by Avicenna, the great Arab physician (AD 980–1087) and, indeed, the authority of Galen continued to dominate medical teaching for a further six centuries.

In the ninth century the embryo of a medical school took form at Salerno. In some remnants of writing at that time, thought to be probably from a student's notebook (Sigerist 1943), there is mention of cautery as a form of treatment: 'apply fire'. Subsequently there followed the establishment of a medical school at Bologna, and at Montpellier in France. A renowned Italian surgeon at that time, William of Salicet (*c.* 1210–1280), wrote the following (Veith 1973):

'But the treatment of cancer is of two sorts; firstly that the affected part be radically and totally cut away with the entire disease by means of a very sharp knife, that the part be subsequently cauterised with the hot iron, and that one proceeds subsequently with substances which soothe the irritation that has been caused by the cautery and favours the separation of the eschar.'

In those mediaeval days, the art of medicine was making its autonomous progress at varying rates in different parts of the world. In the Welsh mountains in Carmarthenshire, the Physicians of Myddvai (Pughe 1861) wrote a book of remedies. Some they may have invented, but probably most were handed down, their origin long forgotten. Some of the remedies combined magic with science, mysterious utterance by the physician being part of the healing art. However, the Physicians of Myddvai do record the use of curettage and cautery in the treatment of anal warts: 'The best way to treat them is to dig them out with cold iron, afterwards cauterising their seat, and anointing the same with honey'. They mention skin cancer, and give as the remedy a caustic application containing arsenic.

Caustic chemicals have for long been a popular remedy for skin cancer. In 1844, E W Tuson FRS, Surgeon to the Middlesex Hospital, stated that 'The use of a paste made with chloride of zinc and flour as an external application in an ulcerated cancer is well known'. Erasmus Wilson, in 'Diseases of the Skin' (1857), gave a good description of basal cell carcinoma, calling it malignant tubercle, and stated firmly that it should be treated by caustic. Zinc chloride, he said, was the most painful, but produced the cleanest sore. He did not mention excision or curettage. Tilbury Fox (1877), in his 'Atlas of Skin Diseases', used the name rodent ulcer. He said that chloride of zinc paste should be used in slighter cases where the knife was objected to, but that if the diseased surface exceeded the area of a sixpenny piece it was safer to remove it by the knife, taking care to apply a thin layer of chloride of zinc paste to the surgical wound when the disease was very extensive.

Culpeper's Complete Herbal (1952) was a collection of remedies in use in the early seventeenth century. Many were for treatment of the skin, for example:

'Agrimony (*Agrimonia Eupatoria*). The leaves and seeds outwardly applied, being stamped with old swine's grease helpeth old sores, cancers, and inveterate ulcers.'
'Alehoof or Ground Ivy (*Gleehoma Hederacea*). The juice of it, boiled with a little honey and verdigris, doth wonderfully cleanse fistulas, ulcers, and stayeth the spreading or eating of cancers and ulcers.'

These quaint mixtures, with a hint of supernatural power about them, had a certain popular appeal and were handed down through generations.

As recently as 1909, the British Medical Association published a book called 'Secret Remedies'. It listed the constituents, after analysis, of current cures which were on sale to the public and which were considered ineffective if not harmful. Among the revelations, zinc chloride was shown to be the active principle in 'the wonderful cures said to be achieved by two persons who resided at Cardigan' in the treatment of cancerous tumours.

In 1936 zinc chloride reappeared in therapeutics, used this time by Dr Mohs in Madison, Wisconsin. He used zinc chloride not simply as a caustic, but as a fixative. When applied to an area of skin, it rendered it dead, bloodless, suitable for precise excision, sectioning and staining (Mohs 1978).

Surgical treatment of skin tumours in the early days is difficult to assess in the absence of accurate diagnosis. The label 'noli-me-tangere' was used, as it was observed that successive recurrences occurred after incomplete removal of some tumours. However Jacques Daviel, a French surgeon known for his work in the treatment of cataract, dared to attempt complete excision of skin cancer, and followed up ten patients who had good results. In 1755 he described these lesions as having a long history, and as he did not mention metastases it might reasonably be assumed that they were basal cell carcinomas. He described in detail the removal of a tumour from the upper eyelid of a nun which had been present for twenty years: 'It began by a small wen, and increased by degrees, so as to very much incommode the patient'. Eight years later he examined her again and found no recurrence of the growth.

In 1827 Arthur Jacob MD, a surgeon to Sir Patrick Dunn's Hospital in Dublin, published his 'Observations respecting an ulcer of peculiar character which attacks the eyelids and other parts of the face'. He noted as characteristic the extraordinary slowness of its progress, the peculiar condition of the edges and surface of the ulcer, the comparatively inconsiderable suffering produced by it, its incurable nature unless by extirpation, and the lack of its contamination of neighbouring lymphatic glands. Each of these characteristics he then examined in more detail: 'The edges are elevated, smooth and glossy, with a serpentine outline; and are occasionally formed into a range of small tubercles or elevations'. After a thorough look from every aspect he concluded that this ulcer was 'not to be confounded with genuine carcinoma, or with the disease called lupus, or noli-me-tangere'. From the dusty accumulation of passing thoughts on tumours of the skin, Jacob drew this clear definition of basal cell carcinoma by its clinical appearance.

In 1886 George Thin, a dermatologist in private practice in London, published 'Cancerous Affections of the Skin'. He found it necessary, in the section on rodent ulcer, to review the history of the condition because the accumulation of literature on the subject from England, Germany and France had brought a welter of opinions and nomenclature. Confusion arose between basal cell carcinoma and squamous cell carcinoma. Thin recognized rodent ulcer as the entity previously described by Jacob (1827) and stated quite firmly that 'there is no other form of cancer in which a cure may be so confidently looked for provided the treatment is undertaken in time'. The treatment he found most satisfactory was excision, but 'in very early stages there is no doubt that a cure may be obtained by scraping out the growth and subsequent cauterisation'. He was sceptical about caustics alone, but of the caustics in use he considered zinc chloride to be the best.

As a nasty reminder of the destruction which basal cell carcinoma can eventually cause, George Thin mentioned the use of prosthetics: 'a vulcanite mask, to conceal the hideous deformity that results from the destruction of the nose and part of the bones of the face, enables the unfortunate victim to appear among his fellows, and to obtain some enjoyment from life'.

After the establishment of basal cell carcinoma as a clinical entity came its definition by microscopic examination – usually credited to Krompecher, a German pathologist. In 1903 he published 'Der Bazalzellenkrebs' which contained illustrations of the histology. Actually, in 1875 Hebra & Kaposi had published an account of the microscopic appearance of 'ulcus rodens' in their book 'Diseases of the Skin', describing 'accumulations of epithelial cells in irregular clumps, or concentrically arranged around a central mass'. Although there has been much study since that time which has concentrated on identifying different histological types of basal cell carcinoma and linking them to different origins, prognosis and treatment, no really useful directive has been produced.

An enlightening concept of the histology is the three-dimensional view presented by Sanderson (1961). He described three main patterns of growth: (1) 'Expanding solid masses whose boundaries are composed of palisaded columnar cells'. (2) 'Thin strands and sheets of cells which invade the surrounding tissue'. (3) 'Piecemeal enclosure of the adjacent connective tissue by outgrowths of the tumour'. The expanding solid masses he likened – in their simplest form – to a string of Chinese lanterns suspended from the epidermis; the thin invasive strands to schools of small fish; and the piecemeal enclosure to a honeycomb.

In 1895 Roentgen observed and identified X-rays. In 1898 the Curies discovered radium. The destructive powers of X-radiation were put to use with enthusiasm. So good were the initial results that, in an attempt to be thorough, larger than adequate dosage was given. In 1900 Stenbeck, from Stockholm, published 'a case of skin cancer, cured by Roentgen-Ray treatment'. This patient had a ten-year history of an ulcerating lesion on the nose, which had been treated twice with cautery. There seems no doubt from the chronic course and description of the lesion that it was a typical rodent ulcer, but there was no biopsy. The patient's dread of surgery 'caused her to seek treatment by Roentgen rays'. Treatment began with 'middle strength X-rays', given daily for 10–12 minutes, with a patient-to-lamp distance of 15–20 cm. After about 35 sessions, and an initial reaction which settled down, healing commenced. At this point radiation was increased to 15 minutes at a 10 cm distance. Complete healing followed. This patient was treated in 1899, a very early record of radiotherapy in skin cancer.

As a therapeutic method radiotherapy was taken up quickly, and in 1901 James Sequeira described 12 cases, the first of which was treated in June 1900. He concluded that the immediate result was all that could be wished for, and he felt justified in recommending the use of X-rays at least in cases in which complete removal by the knife was impracticable.

Not until twenty years later did radionecrosis come to be reconized as a delayed complication of the treatment. In describing radiodermatitis, in 1927, MacCormac said:

'The acute ulcer resulting from an overdose is generally covered with a tough diphtheroid membrane, is remarkably slow to heal, and leaves a pigmented scar behind. Besides this form of immediate reaction, the ill-effects of X-rays may be delayed for months or years, often long after the last dose has been given'.

He went on to describe atrophy, telangiectasis, pigmentation, and ulceration.

Eighty years' experience in the use of radiotherapy has produced much refinement in technique, but radionecrosis can still occur and in the case of basal cell carcinoma another late complication is occasionally seen – that of fresh tumour growth at the site of radiation. X-ray epilation for ringworn in childhood has in some cases been followed by the appearance of multiple basal cell carcinomas on the scalp in adult life, and basal cell carcinomas following radiotherapy to ankylotic spines are well recognized.

A logical method for the removal of basal cell carcinoma is excision, using the technique devised by Dr F Mohs in Madison, Wisconsin, in 1936. Horizontal layers of tumour are removed, the deep surface scanned histologically, and excision repeated until a tumour-free plane is reached. Mohs (1978) now uses a fresh-tissue technique routinely, and employs fixation with zinc chloride only in advanced or complicated cancer. In either method an essential feature is to mark the tissue as it is excised, making it possible to define exactly the site of any tumour present.

Nowadays, incantation as a therapeutic measure has been abandoned. Jacob's (1827) 'ulcer of peculiar character' still warrants that description. Despite increasingly sophisticated methods of destruction, the words of Jacob still apply:

'The sooner it is completely extirpated by the knife, or the actual or potential cautery, the better chance is afforded the patient of relief from a most distressing and fatal malady.'

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